

# Maternal exposure to ethylene glycol monomethyl ether acetate and hypospadias in offspring: a case report

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Ethylene glycol monomethyl ether acetate (EGMEA, or methoxyethylacetate) is used as an industrial solvent. In the organism glycol acetates are easily hydrolysed to the corresponding glycols.<sup>1</sup> The half life of EGMEA (in vitro, with rat plasma) is about 12 minutes.<sup>2</sup> Hence, the toxicological profiles of EGMEA and of its parent substance, ethylene glycol monomethyl ether (EGME), are almost identical.<sup>3</sup> EGME is both teratogenic and fetotoxic in different species.<sup>2,4,5</sup> Mice dosed by mouth during pregnancy (31.25 mg EGME/kg bw) showed skeletal malformations in their offspring. A higher dose (250 mg EGME/kg bw) was acutely toxic (only 130 of 283 litters survived) but induced a large number of severe malformations.<sup>4</sup> Inhalation teratogenicity studies (50 ppm EGME) produced skeletal abnormalities in mice, although less pronounced, and showed the occurrence of unilateral testicular atrophy in the mouse.<sup>5</sup> Skeletal abnormalities were also seen in the rat and teratogenic effects in various organ systems occurred in the rabbit. Thus both substances, on the basis of animal experimentation,<sup>6</sup> were classified as industrial teratogens. EGME is also toxic to the testes and the bone marrow.<sup>2</sup> Human observations of teratogenic effects have not so far been reported. We now report the occurrence of hypospadias in two young boys whose mother was intensively occupationally exposed to EGMEA during both pregnancies.

## Case history

The woman, born in 1959, had worked in an industrial laboratory for lacquers and enamelled wire since 1974. In this laboratory the new lacquers tested contained EGMEA as a main solvent. During her first pregnancy in 1980-1 she cleaned the glassware and other equipment used in the laboratory for at least four hours a day. For cleaning, EGMEA was used as a solvent; flasks were cleaned in a sink by

rinsing with EGMEA. Gloves were usually used but not always.

Cleaning of surfaces, such as laboratory desks, was also performed; for this purpose EGMEA was distributed on a cloth and then spread by rubbing. This was often done without protective gloves. Thus EGMEA was in frequent and direct contact with the skin. The mean daily consumption of EGMEA was about one to two litres. During her second pregnancy in 1983-4 she cleaned the glassware for about one hour a day, generally under a hood. To clean the surfaces in the laboratory, however, EGMEA was used as before. Thus during this second pregnancy direct dermal contact also occurred.

In 1981 a boy of normal birth weight was delivered at term with the following malformations: perineal hypospadias, micropenis, and pronounced bifid type of scrotum. Sex could not be definitely determined without chromosomal analysis. Different medical investigations were performed. Clinical examinations showed no further malformations. Laboratory reports consisted of normal findings: TPHA-test (syphilis), Guthrie's test (inborn errors of amino acid metabolism), TSH-test, meconium test, ketosteroid excretion (metabolites of androgenic steroids), and pregnantriol excretion (metabolite of progesterone). Analysis of the chromosomes showed a normal male karyotype (46xy). An intravenous pyelogram and a cystoscopy performed in 1983 gave normal results.

In 1984 a second boy, again of normal weight, was delivered at term with penile hypospadias and a bifid type of scrotum. All the medical investigations as described above were performed except that cystoscopy was replaced by ultrasonography. No additional pathological results were found. In the following years both children underwent surgery. The perineal and the penile hypospadias were corrected, chordee was removed in both children, and the undescended testes were removed to the scrotum. Additionally, the older child was treated with chorionic gonadotrophin; this treatment led to normal sized testes.

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## Discussion

A young woman was exposed to EGMEA by dermal

contact and probably by inhalation in the course of two pregnancies. In experimental animals EGMEA is teratogenic and toxic to the testes. A high cutaneous absorption of EGMEA in man is also well known.<sup>7</sup> Both children suffered from hypospadias. This malformation is an arrest of development or a failure of closure of the urethral groove, the specific cause of which is unknown.<sup>8,9</sup> Animal experiments point to the influence of the fetal testes in critical stages of the development of the genital tract. For instance, castration of rabbit fetuses on day 21 or 22 results in incomplete masculinisation of the external genitals (hypospadias) and in incomplete development of the prostate or the genital tract, or both.<sup>10</sup> Hypospadias may be associated with further malformations or with different types of intersexes.<sup>9</sup> Few familial cases have been reported.<sup>9</sup> The risk for isolated hypospadias is reported to be between 1 to 300 and 1 to 1800,<sup>8</sup> the risk for a brother of a boy who already suffers from hypospadias is reported to be about 1 to 24.<sup>9</sup> In our case both the family history and medical examinations showed no overt risks other than the pronounced exposure of the mother to EGMEA during fetal development. Thus it seems likely that the hypospadias were actually caused by EGMEA. These cases are the first to be reported that point to the probability of a teratogenic effect of glycol ethers also in man.

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